REMARKS

Claims 1-4, 7, 9-10, 20-22, 25-26, 33-35, 38-39, 46- 47 and 50-51 are currently pending.

THE CLAIMED INVENTION

The invention is directed to novel methods that replenish glutathione (GSH) using sulfhydryl protected glutathione prodrugs. Before Applicants' invention, no one taught or suggested using sulfhydryl protected glutathione prodrugs to replenish GSH in a subject. Applicants were the first to provide experimental evidence that an exogenously administered sulfhydryl protected glutathione prodrug, e.g., L-CySSG, can protect the liver from the toxic insult of acetaminophen, a drug known to severely deplete GSH and elicit hepatotoxicity.

REJECTION UNDER 35 U.S.C. §103(a)

The Examiner rejected claims 1-4, 7, 9-10, 20-22, 25-26, 33-35, 38-39, 46-47 and 50-51 as unpatentable over Demopoulos et al., U.S. Patent 6,159,500 and Eriksson et al., 1970.

Applicants respectfully disagree.

A. THE LEGAL STANDARD FOR ESTABLISHING OBVIOUSNESS UNDER 35 U.S.C. §103

The legal standard for a rejection under §103 is as follows. As set forth in MPEP §2143:

> *To establish a* prima facie *case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.*

The teaching or suggestion to make the claimed combination, and the reasonable expectation of success, must both be found in the prior art, not in the Applicants' disclosure (*In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991)).

Obviousness is a question of law based on findings of underlying facts relating to the prior art, the skill of the artisan, and objective considerations. See *Graham v. John Deere Co.*, 383 U.S. 1, 17, 86 S.Ct. 684, 148 USPQ 459, 467 (1966). To establish a *prima facie* case of obviousness based on a combination of the content of various references, there must be some teaching, suggestion or motivation in the prior art to make the specific combination that was made by the applicant. *In re Raynes*, 7 F.3d 1037, 1039, 28 USPQ2d 1630, 1631 (Fed. Cir. 1993); *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1445 (Fed. Cir. 1992). Obviousness can not be established by hindsight combination to produce the claimed invention. *In re Gorman*, 933 F.2d 982, 986, 18 USPQ2d 1885, 1888 (Fed. Cir. 1991). As discussed in *Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 1143, 227 USPQ 543, 551 (Fed. Cir. 1985), it is the prior art itself, and not the Applicants' achievement, that must establish the obviousness of the combination.

The teachings of the references, their relatedness to the field of the Applicants' endeavor, and the knowledge of persons of ordinary skill in the field of the invention, are all relevant considerations. See *In re Oetiker*, 977 F.2d at 1447, 24 USPQ2d at 1445-46; *In re Gorman*, 933 F.2d at 986-87, 18 USPQ2d at 1888; *In re Young*, 927 F.2d 588, 591, 18 USPQ2d 1089, 1091 (Fed. Cir. 1991). When the references are in the same field as that of the Applicants' invention, knowledge thereof is presumed. However, the test of whether it would have been obvious to select specific teachings and combine them, as did the Applicants, must still be met by identification of some suggestion, teaching, or motivation in the prior art, arising from what the prior art would have taught a person of

ordinary skill in the field of the invention. *In re Fine*, 837 F.2d 1071, 1075, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988).

B. APPLICANTS HAVE MET THE LEGAL STANDARD FOR NONOBVIOUSNESS

Applicants have met the legal standard for nonobviousness because none of the cited references suggest the use of sulfhydryl protected glutathione prodrugs to replenish GSH in a subject as claimed.

U.S. Patent 6,159,500 by Demoupolos et al.

As described in the '500 patent, previous art teaches oral administration of glutathione, in general, to be ineffective (col. 2, lines 3-7 and lines 16-21). Further, the patent describes in col. 2, lines 45-47, that known protocols for direct administration of glutathione, generally, did not provide convenience and high bioavailability. In view of the prior arts' shortcomings, the '500 patent teaches a formulation of glutathione in its reduced form GSH. As described in the'500 patent, the authors emphasize the necessity of the reduced state of glutathione for its administration. (See, for example, col. 17, lines 45-47 and col. 18, lines 7-11).

The '500 patent only teaches the oral administration of a stably reduced glutathione, i.e. GSH. The '500 patent never teaches administration of GSH alone (in view of the problems above) but teaches a formulation comprising GSH and ascorbic acid. Ascorbic acid is a well known antioxidant. Thus, the concurrent administration of ascorbic acid and GSH maintains GSH in its reduced form, i.e., protects its oxidation in the subject to the disulfide form GSSG or CySSG (e.g., col. 18, lines 14-32).

In contrast, the invention requires the direct administration of a sulfhydryl protected glutathione. The '500 patent does not teach or suggest the use of an oxidized (sulfhydryl protected) form of glutathione.

Eriksson, Stellan A. and Bengt Mannervik, "The Reduction of the L-cystein-glutathione mixed disulfide in Rat Liver," FEBS Letters, March 1970, 742:26-28

Eriksson et al. does not teach what the '500 patent fails to teach.

The Office states that Eriksson et al. teaches that CySSG is in equilibrium with GSSG.

Eriksson et al. erroneously show an equation illustrating a chemical "equilibrium" between CySSG and GSH on one side and CySH and GSSG at the other side of the reaction arrows. However, Eriksson et al. does not disclose a chemical equilibrium between CySSG and GSH on one side and CySH and GSSG on the other. Instead, Eriksson et al. describe an enzyme-catalyzed thiol-disulfide exchange reaction (col. 1, lines 17-20). Additionally, data of the subject application fully support such an enzyme-catalyzed reaction and do not support a chemical equilibrium. For an equilibrium reaction either one of L-cysteine or D-cysteine with GSSG should lead to the formation of L- or D-CySSG, respectively, and subsequent release of GSH from either L- or D-CySSG. As can be found at page 8, lines 24-26, of the subject application, GSH appears not to be released from D-CySSG, which suggests a highly specific enzymatic release reaction for L-CySSG, but not D-CySSG and not an equilibrium exchange reaction. Further, the '500 patent teaches no equilibrium between the thiol and disulfide form of glutathione ('500 patent, col. 11, lines 52-54).

Importantly, Eriksson does not suggest that one could use oxidized (sulfhydryl protected) glutathione prodrugs to replenish GSH or that oxidized (sulfhydryl protected) glutathione prodrugs can substitute for a reduced form of GSH.

Traversal

The Office states that it would have been obvious to use any of GSH and GSH's precursors, namely, GSH, GSSG or CySSG, to "replenish the intracellular concentration of such an important small molecule". However, Applicants note that that suggestion is not found in the prior art.

Moreover, GSH and its precursors are not equivalents. For example, Figure 1 of the subject application shows that L-CySSG, a sulfhydryl protected glutathione prodrug, is superior to GSH-OEt, a sulfhydryl unprotected glutathione prodrug, to replenish GSH depletion in ACP-induced hepatotoxicity in mice. Thus, the administration of oxidized (sulfhydryl protected) glutathione led to an unexpected success.

Before Applicants' invention, no one suggested the use of exogenously administered oxidized (sulfhydryl protected) glutathione to replenish intracellular GSH, because oxidized (sulfhydryl protected) glutathione is the product of GSH when protecting cells from oxidative stress, and the cited reference suggests that it is the reduced form (GSH) that should be given and not the oxidized form.

Once in the subject, GSH is, among other reactions, oxidized to GSSG. The oxidized glutathione GSSG is not active towards free radicals itself. However, it can be reduced to GSH via an enzymatic reaction by glutathione reductase and NADPH as coenzyme. As GSSG or other oxidized (sulfhydrate protected) forms of glutathione are not active drugs, they can be named as prodrugs or precursors.

Under normal conditions, reduced glutathione (99% GSH) can be found intracellularly, while four different forms of glutathione occur in (blood) plasma: GSH (thiol) (also referred to herein as reduced glutathione), GSSG (disulfide), CySSG (GSH-L-cysteine complex, disulfide) and GSSPr (GSH-protein complex, disulfide), as stated by the '500

patent in col. 11, lines 13-67. These forms are not in equilibrium, but appear to be in a steady state maintained in part by transport of these compounds between tissues ('500 patent, col. 11, lines 52-54). Oxidative conditions display a depletion of GSH by oxidation, as described above.

Under aggressive oxidative stress, for example after acetaminophen administration, a source of GSH has to be provided in which release of GSH occurs very fast. It has not been obvious to administer oxidized glutathione (GSSG or CySSG) which are discussed as storage forms of GSH. Prior to the present invention, it had not been known whether the enzymatic reduction (or enzyme-catalyzed thiol-disulfide interchange reaction) velocity of GSSG or CySSG would be sufficiently fast and efficient to replenish GSH under strong oxidizing conditions. Additionally, prior to the present application, nothing had been known about the uptake of oxidized forms of glutathione in body.

Contrary to the position of the Office, the '500 patent does not suggest that GSH can be replenished by administering to a subject a GSH ester, and certainly not a sulfhydryl protected glutathione prodrug such as GSSG or CySSG as claimed. This deficiency is not remedied by Eriksson et al.

The mere fact that references can be combined does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F.2d 680, 16 U.S.P.Q.2d 1430, cited in MPEP §2143.01. There must be a reason or suggestion in the art for modifying the prior art other than the knowledge learned from applicants' disclosure[1]. However, the cited references provide none. The primary reference, the '500 patent, teaches the use of stably reduced GSH to replenish GSH. Further, the secondary reference, the Eriksson reference, does not teach or suggest what the primary references fail to teach, namely, the use of sulfhydryl protected glutathione

[1] *In re Dow Chemical Co.*, 837 F.2d 469, 473, 5 USPQ2d 1529, 1532 (Fed. Cir. 1988).

prodrugs to replenish GSH as claimed. Further, there would have been no motivation to substitute GSH of the prior art to the sulfhydryl protected glutathione prodrugs of the claimed methods because it was taught that GSH and sulfhydryl protected glutathione prodrugs are not equivalents. Accordingly, the combination of the primary and secondary references does not and cannot render obvious the claimed methods.

TEACH AWAY

In fact, the '500 patent teaches away from the use of a sulfhydryl protected glutathione prodrug. For example, the '500 patent, in col. 18, lines 43-46, teaches that oxidizing conditions *promote disulfide formation and therefore formation of GSSG* which may *reduce bioavailability* of glutathione and counteract some of the potential benefits of glutathione administration. Thus, the '500 patent clearly "teaches away" from administration of glutathione in its oxidized (sulfhydryl protected) form.

Additionally, the '500 patent "teaches away" from the administration of glutathione esters which are encompassed by another particular embodiment of the present invention (claims 7, 22, 35, and 47). Specifically, the '500 patent describes that glutathione esters are more expensive than glutathione itself and have proven toxic (col. 2, lines 48-52).

Because of the preceding discussion, Applicants request that the Patent Office reconsider and withdraw the various grounds for objection and rejection set forth in the Office Action and earnestly solicit allowance of the claims being examined.

CONCLUSION

If a telephone interview would be of assistance in advancing the prosecution of the subject application, Applicants' undersigned attorney invites the Examiner to telephone her at the number provided below.

No fee is deemed necessary in connection with the filing of this Communication. If any fee is necessary, the Patent Office is authorized to charge any additional fee to Deposit Account No. 50-0306.

Respectfully submitted,

Sarah B. Adriano

Sarah B. Adriano
Registration No. 34,470
SaraLynn Mandel
Registration No. 31,853
Mandel & Adriano
55 So. Lake Ave., Suite 710
Pasadena, California 91101
626/395-7801
Customer No: 26,941